REMARKS

Claims 16-18, 20-24, 26-35, 37-39, 41-46 are pending herein. By this Amendment, Claim 19 is canceled, without prejudice or disclaimer; and Claims 1, 32, and 43 are amended. No new matter is added.

I. First Rejection Under 35 U.S.C. 103(a)

Claims 16-17, 21-28, 31, 33, 35-38, 40-41 and 43 [*sic:* and 19 on page 6 of Office Action] were rejected under 35 U.S.C. 103(a) over Singh et al. (Anal. Chem., 2000) in view of Wu et al. (Letters in Applied Microbiology, 2001). This rejection is respectfully traversed.

A. The 132 Declaration Is Commensurate In Scope With The Claims

The Examiner asserts that the Combined Declaration Under 37 C.F.R. 1.131 and 1.132 filed on February 12, 2008 is not commensurate in scope with the claims because "the instant claims do not recite any limitations with respect to lipid mixtures or the number of amplicons necessary for the assay" or "there are no limitations requiring specific level of detection" (final Office Action at pages 2-3). To the contrary, pending Claim 19 recites the number of nucleic acid segments; Claim 37 recites a detection level; and Claims 44-45 recite phospholipids and a method of encapsulating. Thus, the 132 Declaration is commensurate in scope with the pending claims.

Claim 19 is canceled and its subject matter is incorporated into independent Claim 16. Accordingly, independent Claim 16 is amended to be explicitly commensurate in scope with the Declaration by requiring 50-1,000 nucleic acid segments.

B. The *Prima Facie* Case of Obviousness Has Been Rebutted

The Examiner asserts that it would have been *prima facie* obvious to one of ordinary skill in the art to use the liposomes of Singh et al. with nucleic acid reports as taught by Wu et al. to detect the presence of an analyte with greater sensitivity. The Examiner asserts that the DNA reporters disclosed by Wu et al. enable detection of analytes at low levels because DNA markers improve sensitivity from 100 fold to 1000 fold over standard immunoassay methods (final Office Action at page 8).

The Examiner's rationale is that there is a simple substitution of one known element for another to obtain predictable results or that combining prior art elements according to known methods would yield predictable results. *See* MPEP 2143 which articulates what rationales must be established to support a *prima facie* case of obviousness in view of *KSR*.

In rebutting these rationales, Applicants have demonstrated in the 131/132 Declaration that: (1) one of ordinary skill in the art could not have encapsulated nucleic acid segments within the liposomes of Singh et al.; and (2) the claimed invention achieves superior and unpredicted detection results.

1. The Combination of Singh et al. and Wu et al. Would Render An Inoperable Method

As noted in the 131/132 Declaration, the method of liposome formation in Singh et al. is only capable of encapsulating about 4 amplicons per liposome, which is unacceptable for the claimed method for detecting an analyte with an immunoliposome-nucleic acid amplification assay. Contrary to the Examiner's reasoning, one of ordinary skill in the art could not simply "substitute DNA markers [of Wu] for the Rhodamine marker of Singh..." (Office Action dated October 12, 2007 on page 10).

It is axiomatic that if a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. See MPEP 2143.01. In view of the 131/132 Declaration, Applicants have established that trying to incorporate nucleic acid segments into the liposomes of Singh et al. would render an inoperable method for detecting an analyte with an immunoliposome-nucleic acid amplification assay.

2. The Claimed Invention Achieves Superior Detection Results

The results of the claimed invention could in no way have been predicted. Even if there were a 100 to 1000 fold improvement in the results of Singh et al., as asserted by the Examiner, this would at best lead to a detection level of 1×10^{-13} moles (an 1,000 fold improvement of 1×10^{-10} moles). However, the claimed ILNAA assay would still be 5 Billion times more sensitive! *See* Table on page 6 of the 131/132 Declaration.

Accordingly, in view of the 131/132 Declaration, Applicants have rebutted the Examiner's *prima facie* case of obviousness. As stated in MPEP 2145:

> If a *prima facie* case of obviousness is established, the burden shifts to the applicant to come forward with arguments and/or evidence to rebut the *prima facie* case. See, e.g., In re *Dillon,* 919 F.2d 688, 692, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990). Rebuttal evidence and arguments can be presented in the specification, *In re Soni*, 54 F.3d 746, 750, 34 USPQ2d 1684, 1687 (Fed. Cir. 1995), by counsel, *In re Chu*, 66 F.3d 292, 299, 36 USPQ2d 1089, 1094-95 (Fed. Cir. 1995), or by way of an affidavit or declaration under 37 CFR 1.132...
>
> When considering whether proffered evidence is commensurate in scope with the claimed invention, Office personnel should not require the applicant to show unexpected results over the entire range of properties possessed by a chemical compound or composition. See, e.g., *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987). Evidence that the compound or composition possesses superior and unexpected properties in one of a spectrum of common properties can be

> sufficient to rebut a *prima facie* case of obviousness. *Id.* (Emphasis added).

(Emphasis added).

Finally, Applicants have noted that Wu et al. requires DNA-antibody conjugates. The 100 to 1000 fold improvement of Wu et al. is a result of comparing DNA-antibody conjugates to ELISA assays in which an enzyme is conjugated to an antibody. Wu et al. also discloses immuno-PCR techniques, which require conjugation of DNA to antibodies or to streptavidin. *See* paragraph [0011] of the specification. There is no teaching or suggestion in any of the cited references to decouple DNA nucleic acid segments from an antibody or enzyme and to use them individually in an assay.

As the *prima facie* case of obviousness has been rebutted, reconsideration and withdrawal of the rejection as to Claims 16-17, 21-28, 31, 33, 35-38, 40-41 are respectfully requested.

C. Claim 43 Is Not Obvious In View of The Cited Art

Regarding Claim 43, the Examiner has not cited to any teaching to render this method obvious. *See* final Office Action at pages 3 and 6. Neither Singh et al. nor Wu et al. teaches or suggests exposing the receptors to a target analyte, causing aggregation of the receptors within the plane of the liposomal bilayers, wherein the aggregation causes the liposomal bilayers to become unstable leading to spontaneous rupture of the liposomal bilayers. In contrast, Singh et al. requires lysing liposomal bilayers to release the nucleic acid segments (page 6022).

Thus, one of ordinary skill in the art would not have practiced the claimed methods in view of the combined teachings of Singh et al. and Wu et al. Reconsideration and withdrawal of the rejection of Claim 43 are respectfully requested.

II. Other Rejections Under 35 U.S.C. 103(a)

Claim 18 was rejected under 35 U.S.C. 103(a) over Singh et al. in view of Wu et al. and further in view of Cao et al. (The Lancet, 2000). This rejection is respectfully traversed.

Cao et al. does not overcome the deficiencies of Singh et al. and Wu et al. Cao et al. does not teach or suggest a method for detecting an analyte with an immunoliposome-nucleic acid amplification assay comprising encapsulating 50 to 1,000 identical nucleic acid segments within closed shell liposomal bilayers. Cao et al. also does not teach or suggest the superior and unexpected detection results achieved by the present invention. Thus, one of ordinary skill in the art would not have practiced the claimed methods in view of the combined teachings of Singh et al., Wu et al., and Cao et al. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 20, 42, and 46 were rejected under 35 U.S.C. 103(a) over Singh et al. in view of Wu et al. and further in view of U.S. Patent No. 4,704,355 (Bernstein). This rejection is respectfully traversed.

Bernstein does not overcome the deficiencies of Singh et al. and Wu et al. Regarding Claims 20 and 46, Bernstein does not teach or suggest a method for detecting an analyte with an immunoliposome-nucleic acid amplification assay comprising encapsulating 50 to 1,000 identical nucleic acid segments within closed shell liposomal bilayers. Further, Bernstein does not teach or suggest the superior and unexpected detection results achieved by the present invention.

Regarding Claim 42, contrary to the Examiner's assertion, Bernstein does not teach or suggest that an immobilized target analyte is immobilized on magnetic micro-particles or a micro-fabricated device. Bernstein merely discloses that a DNA probe analyte may be immobilized on a "particle" (col. 5, lines 30-35). Thus, one of ordinary skill in the art would not have practiced the claimed method in view of the combined

teachings of Singh et al., Wu et al., and Bernstein. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 29-30 were rejected under 35 U.S.C. 103(a) over Singh et al. in view of Wu et al. and further in view of U.S. Patent No. 6,503,452 B1 (Boxer et al.). This rejection is respectfully traversed.

Boxer et al. discloses a surface detector array device suitable for use with a biosensor. The device is formed of a substrate having a surface defining a plurality of distinct bilayer-compatible surface regions separated by one or more bilayer barrier regions. The bilayer-compatible surface regions carry on them, separated by a film of aqueous, supported fluid bilayers. The bilayers may contain selected receptors or biomolecules (Abstract). Boxer et al. discloses attaching a biomolecule to a liposome through a spacer arm such as polyethylene glycol to form modified bilayers (col. 13, lines 2-8 and col. 14, lines 4-22).

Boxer et al. does not teach or suggest reducing non-specific binding of the liposomal bilayers on an immobilizing substrate by attaching polyethylene glycol to the surface of the liposomal bilayer, as recited in Claim 29. In contrast, the substrate 22 in Boxer is separated from lipid bilayer expanse 30 by an interposed aqueous film 32 (FIG. 1).

Further, Boxer et al. does not teach or suggest varying the length of a spacer arm used to attach the receptors to the liposomal bilayers, as recited in Claim 30. There is no teaching at col. 14, lines 8-12 to vary the length of a spacer arm as asserted by the Examiner. One of ordinary skill in the art would not have practiced the claimed methods in view of the combined teachings of Singh et al., Wu et al., and Boxer et al. Reconsideration and withdrawal of the rejection are respectfully requested.

Claim 31 was rejected under 35 U.S.C. 103(a) over Singh et al. in view of Wu et al. and further in view of Huang et al. (Biotechniques, 1996). This rejection is respectfully traversed.

Huang et al. does not overcome the deficiencies of Singh et al. and Wu et al. Huang et al. discloses using DNAse to remove contaminating DNA (which acts as a secondary competitor) from RNA in an RNA-PCR study. There is no physical separation of the DNA and RNA sequences.

There is no teaching to use DNAse to degrade background DNA in an assay while leaving identical reporter DNA segments intact within liposomes. There is no recognition or appreciation that DNA segments are protected from degradation because the DNAse enzyme cannot cross the liposomal bilayer. In view of the teachings of Huang et al., one of ordinary skill in the art would not have been motivated to degrade contaminating DNA outside of a liposome by adding DNAse to the assay solution and then to amplify DNA segments released from liposomes, for example, by DNA-PCR.

In addition, Huang et al. does not overcome the deficiencies of Singh et al. and Wu et al. Huang et al. does not teach or suggest a method for detecting an analyte with an immunoliposome-nucleic acid amplification assay comprising encapsulating 50 to 1,000 identical nucleic acid segments within closed shell liposomal bilayers. Huang et al. also does not teach or suggest the superior and unexpected detection results achieved by the present invention. Thus, one of ordinary skill in the art would not have practiced the claimed methods in view of the combined teachings of Singh et al., Wu et al., and Huang et al. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 44-45 were rejected under 35 U.S.C. 103(a) over Singh et al. in view of Wu et al. and further in view of Bailey et al. This rejection is respectfully traversed.

Bailey et al. does not overcome the deficiencies of Singh et al. or Wu et al. Regarding Claim 44, Bailey et al. does not teach or suggest a method for detecting an analyte with an immunoliposome-nucleic acid amplification assay comprising encapsulating 50 to 1,000 identical nucleic acid segments within closed shell

liposomal bilayers. Bailey et al. does not teach or suggest the superior and unexpected detection results achieved by the present invention.

Regarding Claim 45, none of the cited references teaches or suggests exposing the receptors to a target analyte, causing aggregation of the receptors within the plane of the liposomal bilayers, wherein the aggregation causes the liposomal bilayers to become unstable leading to spontaneous rupture of the liposomal bilayers, and release of the nucleic acid segments, as recited in independent Claim 43 from which Claim 45 depends.

Thus, one of ordinary skill in the art would not have practiced the claimed methods in view of the combined teachings of Singh et al., Wu et al., and Bailey et al. Reconsideration and withdrawal of the rejection are respectfully requested.

III. Additional Rejections Under 35 U.S.C. 103(a) Antedated

Claim 32 was rejected under 35 U.S.C. 103(a) over Singh et al. in view of Wu et al. and further in view of *newly-cited* US Patent Application Publication 2004/0258570 (Beebe et al.). This rejection is respectfully traversed.

Beebe et al. was published on December 23, 2004 and has an effective filing date of November 4, 2002. Accordingly, Beebe et al. is a 102(e) reference, as the present application has a filing date of January 20, 2004.

As noted in the attached Supplemental 131 Declaration, which incorporates all the facts and exhibits of the original Combined Declaration Under 27 C.F.R. 1.131 and 1.132, the present invention was conceived of prior to 2000 and reduced the invention to practice in September 2002. Thus, Beebe et al. is not prior art to the present application. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 34 and 39 were rejected under 35 U.S.C. 103(a) over Singh et al. in view of Wu et al. and further in view of *newly-cited* US Patent Application Publication 2005/0079520 (Wu et al. '520). This rejection is respectfully traversed.

Wu et al. '520 was published on April 14, 2005 and has an effective filing date of July 21, 2003. Accordingly, Wu et al. '520 is a 102(e) reference. As noted, the present invention was conceived of prior to 2000 and reduced the invention to practice in September 2002. Thus, Wu et al. '520 is not prior art to the present application. Reconsideration and withdrawal of the rejection are respectfully requested.

IV. CONCLUSION

In view of the remarks above, Applicants respectfully submit that the present application is in condition for allowance. If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

Respectfully submitted,

/Warren Zitlau/

Warren A. Zitlau
Registration No. 39,085

CAHN & SAMUELS, LLP
1100 17th Street, NW, Suite 401
Washington, D.C. 20036
Telephone: (202) 331-8777

Date: September 3, 2008